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Granulocytic Leukemoid Reactions Associated with Malignant Disease

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IN GRANULOCYTIC LEUKEMOID reactions associated with malignant disease, the lung, stomach and breast have been reported as the most frequent primary sites, but neoplasms of the kidney, gallbladder, pancreas and liver have also been implicated. These reactions usually can be differentiated from chronic myelocytic leukemia clinically, but leukocyte counts in excess of 100,000 per cu mm may be troublesome. The unusual counts could result from overproduction with an increase in leukocytes throughout the body, or merely from redistribution due to breakdown of the normal bone marrow-blood barrier.

This report describes a patient with a giant cell carcinoma of the lung and a pronounced leukemoid reaction without demonstrable bone marrow metastasis. Hematologic data on three patients with similar conditions are given. Determinations of alkaline phosphatase in neutrophilic leukocytes and absolute basophil counts were helpful in arriving at the correct diagnosis. Data from a cursory review of the literature on leukemoid reactions associated with carcinoma are summarized.

REPORT OF A CASE

An 85-year-old widow was admitted to San Francisco General Hospital on March 19, 1962, one day after the onset of chills and fever. A month pre-

viously she had felt a sharp sudden mid-back pain after turning quickly. Transient "paralysis" of the right arm subsided spontaneously. This was followed by progressive weakness. No history of cough or dyspnea was elicited.

On admission the temperature was 102.4°, the pulse rate 108 and respirations 24 per minute. The blood pressure was 108/40 mm of mercury. The patient appeared acutely and chronically ill and in moderate respiratory distress. A soft lymph node 3 cm in diameter was felt in the left supraclavicular area. Subcrepitant rales were heard in the left posterior lung base. No abnormalities were noted on examination of the abdomen and the heart.

Initial laboratory data included a hematocrit of 33 per cent, a leukocyte count of 48,000 per cu mm with 84 per cent mature neutrophils, 6 per cent banded forms, 8 per cent lymphocytes and 2 per cent monocytes; no myelocytes were seen. An x-ray film of the chest showed a 4-cm circumscribed spherical density in the superior segment of the left lower lobe with a fluffy left lower lobe infiltrate. There was no evidence of osseous metastasis in the ribs, thoracic vertebral column, scapulae, clavicles or the proximal halves of the humeri. No further skeletal x-ray examinations were done. Results of urinalysis were within normal limits. The blood urea nitrogen was 17 mg per 100 ml, the alkaline phosphatase was 14 Bessie-Lowry units (normal range for adults 0.8 to 3.0 units), and lactic acid dehydrogenase was 225 units (normal up to 110 units). Six blood cultures showed no growth. Results of skin tests for tuberculosis, coccidioidomycosis and histoplasmosis were negative.

The patient was treated with antibiotics but continued to be febrile throughout her entire stay in hospital. A lymph node biopsy showed malignant cells of undetermined type. Leukocyte content rose to 188,000 per cu mm on the 11th hospital day (for the differential count at that time see Table 1, Case 20). At this time the hemoglobin was 8.8 gm per 100 cc, erythrocytes numbered 3,390,000 per cu mm, the hematocrit was 33 per cent, reticulocyte count 1.9 per cent and platelet count 491,000. Toxic granules were seen in many leukocytes; all neutrophils were strongly positive for alkaline phosphatase;* rare nucleated red blood cells were seen on the peripheral smear. A sternal marrow aspirate was hypercellular; mature granulocytic elements predominated, many showed toxic granulations. No

*The alkaline phosphatase in mature neutrophils and neutrophil bands in this case and 3 other cases (see Table 2) was stained by the modified Gomori's method¹² and graded as follows:

One plus: faint perinuclear clumping of the black cobalt sulfide.

Two plus: considerable precipitate in the cytoplasm, but with clear areas remaining.

Three plus: cytoplasm loosely filled with fine to coarse granules.

Four plus: cell cytoplasm jet-black, with no evidence of clumping and no clearing visible.

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malignant cells were seen. The patient died on the 13th hospital day.

At autopsy, two large, round subcutaneous masses approximately 10 cm in diameter were found in the left neck and between the scapulae. They invaded the deep tissues and the neighboring bone but did not involve the epidermis. There were also enlarged lymph nodes in the left axilla, above the left clavicle and in the left anterior cervical region. There was a soft, round, 4-cm, yellowish white tumor in the upper segment of the left lower lobe of the lung, encroaching upon the corresponding bronchus.

Microscopic examination of the tumor showed it to be composed of extremely pleomorphic epithelial cells, with many bizarre giant forms containing finely vacuolated amphophilic cytoplasm and large single or multiple pale nuclei with prominent nucleoli and peripherally clumped chromatin. Mitoses were frequent. Intercellular bridges were not seen and there was no gland formation, but in some areas the tumor was growing in an alveolar pattern. Special stains (PAS-digested and colloidal iron) did not show any intracytoplasmic or interstitial mucous material. Occasionally, carcinomatous emboli were found in the adjacent small venules, and in the more distant lung parenchyma there were clusters of malignant cells reminiscent of carcinomatous pneumonia. The adjacent bronchial lymph nodes were replaced by metastatic tumor.

The liver, weighing 2,100 gm, was massively involved by partially necrotic tumor extending from the left lobe of the liver to the gastric wall and toward the splenic hilus. Sections of the metastatic lesions in the liver, cervical and axillary lymph nodes, left adrenal gland and subcutaneous mass from the back showed the same histological pattern as the primary lung tumor. The spleen was not enlarged; the microscopic examination showed

TABLE 1.—Granulocytic Leukemoid Reaction in Malignant Disease

Patient	Tumor		Leukocytes per cu mm	Blood					Bone Marrow		Author	
	Primary	Metastasis		Poly.	Band	Myelo- cyte	Blast.	Eosin.	NR	Source		Metastasis
1.	Lung.....		50,000	Kappis ⁶ (1907)	
2.	Breast.....	Lung.....	120,000	92	0	4	0	0	X	A.	No	Krumbhar ⁸ (1926)
3.	Liver.....	Lymph nodes.....	34,000	17	25	14	0	27	X	A.	No	Sonnenfeld ¹¹ (1929)
4.	Stomach.....	None.....	125,000	28	39	19	0	1	X	A.	No	Sonnenfeld ¹¹ (1929)
5.	Mediastinal carcinoma.....	Liver, spleen.....	180,000	85	0	12	0	0	0	A.	No	Jackson ⁵ (1937)
6.	Lung.....	Lymph nodes, liver, adrenal, kidney, pancreas.....	116,000	85	0	0	0	1	X	A.	No	Jackson ⁵ (1937)
7.	Stomach.....	None.....	110,000	94	0	2	0	0	+	A.	No	Meyer & Rotter ⁹ (1942)
8.	Stomach.....	Spleen, liver, lymph nodes.....	193,000	78	11	9	0	0	0	A.	No	Meyer & Rotter ⁹ (1942)
9.	Lung.....	Adrenal.....	112,500	47	46	3	0	0	0	A.	Yes	Hinshaw & Hoxie ⁴ (1949)
10.	Lung.....	None.....	90,000	31	63	0	0	2	0	A.	No	Fahey ¹ (1951)
11.	Lung.....	Lymph nodes, liver.....	116,000	47	46	0	0	2	X	A.	No	Fahey ¹ (1951)
12.	Lung.....	Lymph nodes, liver, spleen, adrenal.....										
13.	Lung.....	Lymph nodes.....	58,800						X	A.	Yes	Fahey ¹ (1951)
14.	Kidney.....	Lung, thyroid, liver, adrenals, lymph nodes.....	51,000	93	0	6	1	0	+	A.	No	Fahey ¹ (1951)
15.	Gallbladder.....	Liver, lymph nodes.....	67,000	82	9	0	0	1	X	A.	Yes	Hensler ³ (1953)
16.	Gallbladder.....	Liver, kidney.....	39,400	44	21	5	0	20	0	A., As.	Yes	Knick & Schilling ⁷ (1960)
17.	Pancreas.....	Liver, lymph nodes.....	42,400	85	7	0	0	1	0	A., As.	No	Knick & Schilling ⁷ (1960)
18.	Lung.....	Liver, lymph nodes.....	45,800	81	8	0	0	3	0	A., As.	Yes	Knick & Schilling ⁷ (1960)
19.	Kidney.....	Adrenals.....	94,000	71	14.5	0	0	0	X	A., As.	No	Zarafonitis & Joseph ¹³ (1961)
20.	Kidney.....	Lymph nodes, bone marrow.....	52,000	83	13	0	0	0	0	A., As.	Yes	Reiss, O. ¹⁰ (1962)
21.	Liver.....	Lymph nodes, adrenal, skin, liver.....	188,000	86.5	6	6	0	0	0.5	A., As.	No	This study
22.	Kidney.....	Lymph nodes, liver, spleen, lung adrenal, pancreas, vertebral marrow.....	76,000	75	20	3	0	0	0	A., As.	No	This study
23.	Thyroid.....	Lymph nodes, lung, heart.....	140,500	85	5	0	0	0	0	A., As.	Yes	This study
			60,000	84	10.5	0	0	0	.25	A., As.	No	This study

X = no mention
NR = Nucleated erythrocytes per 100 leukocytes

+ = present
O = not found

A. = Autopsy
As. = Aspiration

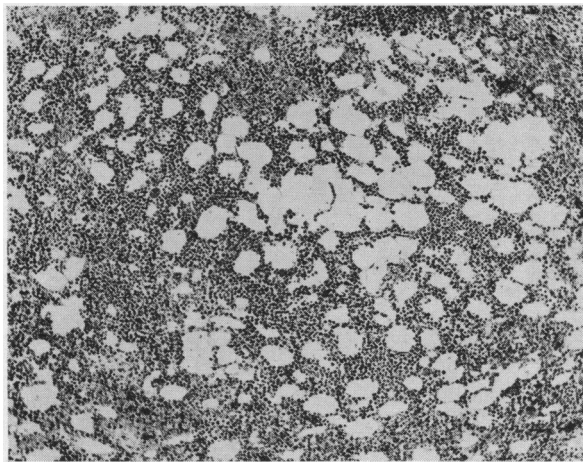


Figure 1.—Bone marrow aspirate, showing granulocytic hyperplasia and preservation of fat spaces. Hematoxylin and eosin stain ($\times 100$).

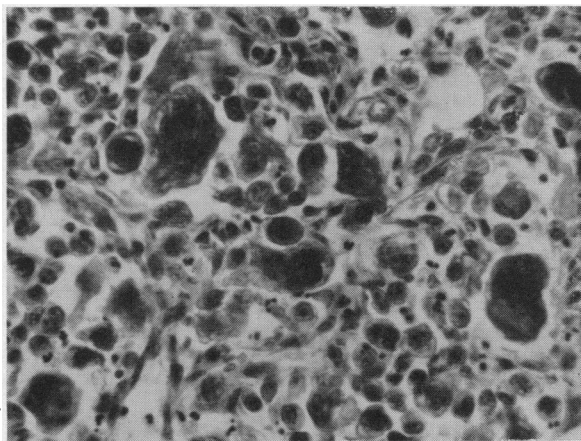


Figure 2.—Section of primary giant cell carcinoma of the lung; note sprinkling of neutrophils throughout the tumor ($\times 475$).

many neutrophils in the red pulp, and occasional nucleated red cells and megakaryocytes. Gross examination of the cranium, vertebral column, ribs and sternum revealed no metastatic lesions. The vertebral rib and sternal bone marrow were soft and dark red. The microscopic examination of the sternal and vertebral sections did not show any metastasis. There was only moderate bone marrow hyperplasia, with preservation of many small fat spaces. The final major pathological diagnosis was 1. Giant cell carcinoma of lung (upper segment of the left lower lobe) with metastasis to the liver and periportal lymph nodes and invasion of the stomach wall and splenic hilus. Metastases to the left adrenal gland, cervical and axillary lymph nodes and deep subcutaneous tissues of the back. 2. Leukemoid reaction. 3. Arterial thrombosis, left kidney, with cortical infarct (1 x 1 cm).

Table 1 summarizes the pertinent data from 23 cases noted in a limited review of the literature and

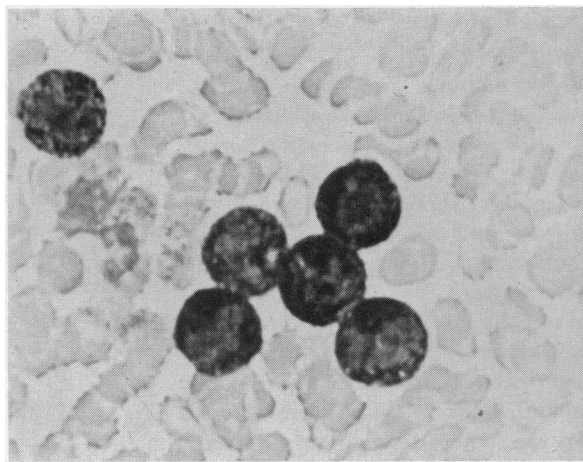


Figure 3.—Peripheral blood stained to show alkaline phosphatase content of cells. Note strongly positive (3+ to 4+) neutrophils and bands ($\times 950$).

includes four observed by us. Table 22 shows, in addition, the diagnostic value of total basophil counts and alkaline phosphatase stains, as seen in those four cases. In Table 3 the data from six patients with chronic myelogenous leukemia are shown to contrast the different values of basophil counts and alkaline phosphatase stains particularly.

DISCUSSION

Certain hematologic features are helpful in distinguishing granulocytic leukemoid reactions from chronic myelocytic leukemia. The blood in leukemoid reactions shows predominantly polymorphonuclear cells. The alkaline phosphatase content of neutrophilic leukocytes and banded forms is strongly positive, basophils are decreased and there may be toxic granulation, cytoplasmic vacuoles and indistinct nuclear membranes. Pronounced eosinophilia is seen occasionally. Nucleated red cells are not particularly prominent. The marrow shows less overall hyperplasia and less increase in myeloid erythroid ratio than that in chronic myelocytic leukemia. In chronic myelocytic leukemia more primitive granulocytes are seen, the alkaline phosphatase reaction is usually negative and the number of basophils is greatly increased.

Leukemoid reactions often occur without demonstrable bone marrow involvement by the cancer. In 12 of the 19 reviewed cases and in three of the four that we observed, no marrow metastasis was reported at autopsy; however, a complete post-mortem examination of the skeleton was seldom carried out.

The lung appears to be the most common primary site in patients with leukemoid reactions associated with cancer; it was involved in nine of the twenty-three cases described here. Lymph nodes were the most common secondary sites and were

TABLE 2.—Blood Features in Leukemoid Reaction

Case No.	WBC ×1000 per cu mm	PMN Per Cent	NF Per Cent	MM Per Cent	M Per Cent	Bl. Per Cent	Eo. Per Cent	Baso. Per Cent	Lymph. Per Cent	Mono. Per Cent	Alk. Phos.	Baso. per cu mm	BM NR
20.....	60	84	10.5	0	0	0	0	0	3	2.5	3-4+	0	244
21.....	76	75	19	3	0	0	0	1	1	1	3-4+	145	236
22.....	140	85	5	0	0	0	0	0	9	1	3-4+	5	106
23.....	188	86.5	6	1.5	4.5	0	0	0	1	0.5	3-4+	0	206

PMN=Polymorphonuclear
NF=Non-filamented cell (stab)
MM=Metamyelocytes
BM NR=Bone marrow nucleated erythrocytes per 1000 leukocytes

M=Myelocytes
Bl=Blasts
Eo=Eosinophils

Baso=Basophils
Lymph=Lymphocytes
Mono=Monocytes

TABLE 3.—Blood Features in Chronic Myelocytic Leukemia

Pt.	WBC ×1000 per cu mm	PMN Per Cent	NF Per Cent	MM Per Cent	M Per Cent	Bl. Per Cent	Eo. Per Cent	Baso. Per Cent	Lymph. Per Cent	Mono. Per Cent	Alk. Phos.	Baso. per cu mm	BM NR
A	21.2	52.5	14.5	6.5	12	0	2	3.5	5.5	3.5	0-1+	394	114
B	53	40	19.5	17.5	9.5	0	1.5	7	4	1	0-1+	1,071	52
C	74.5	40	20	13	4	0	0	3	15	5	0-1+	1,695	68
D	83.5	25.5	5	6.5	27.5	6.5	1	1.5	25.5	1	0-1+	668	20
E	99.6	45.6	21	11	11.6	1.6	0.4	1.4	4.8	2.6	0-1+	2,360	24
F	147	12.5	33	7	17	0	1.5	14.5	12	2.5	0-1+	12,450	83

PMN=Polymorphonuclear
NF=Non-filamented cell (stab)
MM=Metamyelocytes
BM NR=Bone marrow nucleated erythrocytes per 1000 leukocytes

M=Myelocytes
Bl=Blasts
Eo=Eosinophils

Baso=Basophils
Lymph=Lymphocytes
Mono=Monocytes

involved in 14 of 23 cases; liver metastasis was present in 11 cases. (See Table 1.)

The moderate degree of marrow hyperplasia, even with very high leukocyte count and the lack of extramedullary granulopoiesis in most cases, suggests that leukemoid reactions may result from an increase in the intravascular leukocyte compartment, rather than from an increase in total body leukocytes. Since a complete autopsy search for osseous metastasis is seldom done, it is difficult to make any definite statement regarding the bone marrow involvement; it appears, however, that in the reported 23 cases the bone marrow was infrequently involved.

SUMMARY

A case of leukemoid granulocytic reaction associated with a giant cell carcinoma of the lung is reported, and hematologic data from three similar patients are appended and compared with data on six cases of chronic myelogenous leukemia. In a limited review of the literature reports of 19 additional cases were found. The characteristic blood picture of leukemoid reactions includes the predominance of polymorphonuclear cells, a very low basophil count and strongly positive alkaline phosphatase stain.

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One-Stage Resection of Seven Arterial Aneurysms

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THE FINDING of multiple arterial aneurysms in arteriosclerotic patients is no longer unusual. In addition to the case here reported, I have operated upon one patient with a large abdominal aortic aneurysm associated with large, bilateral, iliac and hy-

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